

USE OF CHOLINESTERASE INHIBITORS FOR TREATING ATTENTION DEFICIT DISORDERS

5        The present invention relates to a method of combatting attention deficit disorders (hereinafter referred to as ADD). In particular, the invention relates to the use of a pharmaceutically acceptable cholinesterase inhibitor in the manufacture of a  
10      medicament for use in combatting ADD.

Attention deficit disorders affect children, adolescents and adults affecting up to 10% of children and at least 2% of adults. The childhood condition is often known as attention-deficit hyperactivity disorder (ADHD). Symptoms usually first manifest between the ages of 2 - 5. These children have a short attention span, motor hyperactivity, and are disorganised, forgetful and impulsive. ADHD can have a serious effect on the child's academic progress and performance and causes stress to family and teachers and difficulties in interacting with the child's peer group. The condition can persist into adult life. In adults, the major symptoms include distractibility, disorganisation and accident proneness. The condition in adults and children causes serious disruption to normal lifestyle patterns, and creates great stresses to all aspects of daily life, in the home, the workplace and in social situations. ADD as used herein covers both the adult and child forms of the condition, as well as hyperkinetic disorders and disorders which include any of the characterising criteria of the American Psychiatric Association's DSM-IV Classification of the disorders.

Various therapies have been proposed but have not proved satisfactory, due *inter alia* to lack of efficacy and/or undesirable side effects. Stimulants such as dexamphetamine, methylphenidate and pemoline have been

used clinically in the management of ADD. Whilst they have been found to improve the primary manifestations such as motor activity, distractability and impulsivity in some sufferers, their side effects including 5 anorexia, delayed onset of sleep, mood changes and exacerbation of pre-existing psychotic symptoms together with the possible potential for abuse, limits their utility. Other classes of drug such as tricyclic antidepressants have been suggested in the literature 10 but are not generally regarded as being effective agents for the management of ADD. There is accordingly a need for a new therapeutic method for the management of ADD. The present invention provides such a method.

Thus we have surprisingly found that cholinesterase 15 inhibitors such as galantamine can effectively combat ADD.

According to one aspect, the present invention provides a method of combatting ADD comprising administering to a subject a pharmaceutically acceptable 20 cholinesterase inhibitor.

According to a related aspect, the invention provides the use of a pharmaceutically acceptable cholinesterase inhibitor in the manufacture of a medicament for combatting ADD.

As used herein the term 'combatting' includes both 25 therapy and prophylaxis.

The invention encompasses the use of any cholinesterase inhibitor, provided of course that it is pharmaceutically acceptable.

Examples of cholinesterase inhibitors which may be 30 used according to the invention include, but are not limited to, physostigmine, tacrine and tacrine analogues, fasiculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil 35 and pro-drugs of any of these in which the inhibitor is modified in accordance with principles of pro-drug construction known in the art. Examples of such

- 3 -

modifications include the introduction of hydrophilic or lipophilic groups to enhance solubility, or penetration through cell membranes, respectively.

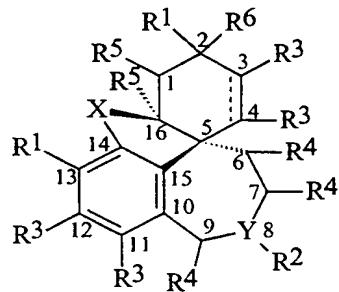
5 Preferred cholinesterase inhibitors for use according to the invention are acetylcholinesterase inhibitors, particularly those which are capable of crossing the blood brain barrier.

10 Particularly preferred cholinesterase inhibitors for use according to the invention include galantamine, epigalantamine and norgalantamine, and analogues, salts 15 and derivatives of any of these. Galantamine was previously known as galanthamine. It is a tertiary alkaloid which can be extracted from various snowdrop bulbs e.g. the Caucasian snowdrop galanthus woronowii (Amaryllidaceae) and related species and daffodil bulbs or made by chemical synthesis. It has a 20 high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. It is active substantially selectively at nicotinic receptor sites with substantially little effect on muscarinic receptor sites.

Particularly preferred cholinesterase inhibitors for use in the invention are galantamine and its derivatives of formula (I):

25

30



35

wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R<sub>1</sub> is

independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C<sub>1-6</sub>alkoxy, alkylthio, aryloxy, arylthio, R<sub>3</sub>-5 substituted aryloxy, R<sub>3</sub>-substituted arylthio, aralkoxy, an optionally R<sub>3</sub>-substituted aliphatic or aryl carbamyl group, aralkylthio, R<sub>3</sub>-substituted aralkoxy, R<sub>3</sub>-substituted aralkylthio, aryloxymethyl, R<sub>3</sub>-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted 10 alkanoyloxy, benzoxyloxy, R<sub>3</sub>-substituted benzoxyloxy, aryloxycarbonyl and R<sub>3</sub>-substituted aryloxycarbonyl,

R<sub>2</sub> is selected from hydrogen, straight or branched chain C<sub>1-6</sub>alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, 15 alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R<sub>3</sub>-substituted phenyl, alkylphenyl, R<sub>3</sub>-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl, thenyl, 20 pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R<sub>3</sub> is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, 25 aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylarnino, N-alkarylarnino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R<sub>4</sub> is independently selected from hydrogen, 30 halo, trifluoromethyl or C<sub>1-4</sub>-alkyl,

each R<sub>5</sub> is independently selected from hydrogen or hydroxymethyl,

R<sub>6</sub> is hydrogen or C<sub>1-6</sub>alkyl, or when R<sub>1</sub> at carbon atom 2 is hydroxyl, R<sub>6</sub> may be a moiety of formula I 35 wherein R<sub>6</sub> is hydrogen and R<sub>1</sub> is a linking bond; or

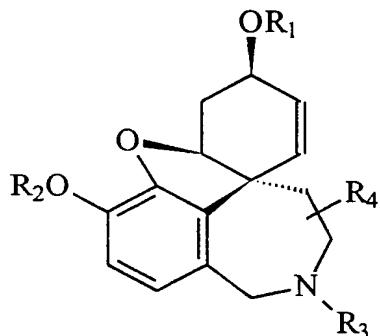
R<sub>1</sub> at carbon atom 2 and R<sub>6</sub> may jointly form semicarbazone,

- 5 -

X is oxygen or NR<sub>3</sub>,  
 Y is nitrogen or phosphorus,  
 and methylenedioxy derivatives thereof and  
 pharmaceutically acceptable acid addition salts thereof.

5 Of the compounds of formula I which may be used in  
 the method of the invention, preferred compounds are  
 those in which the alkyl moieties contain 1 to 8 carbon  
 atoms, halogen atoms are preferably fluorine, bromine,  
 chlorine, aryl moieties are preferably phenyl,  
 10 cycloalkyl groups are preferably 3- to 7-membered rings,  
 especially cyclopropyl or cyclobutyl, acyl groups are  
 preferably lower alkanoyl groups and heteroaryl moieties  
 are preferably 5- to 8-membered rings, e.g., thienyl,  
 furyl, pyridyl, pyrrolyl, or pyrazinyl.  
 15 Preferred compounds of formula I are the compounds  
 of formula II

20



25

II

wherein R<sup>1</sup> and R<sup>2</sup> which may be the same or different  
 each represents a hydrogen atom or an acyl group, such  
 30 as a lower alkanoyl group, e.g. an acetyl group or a  
 straight-chained or branched alkyl group, e.g. methyl,  
 ethyl, propyl, or isopropyl;

R<sup>3</sup> is a straight or branched chain alkyl, alkenyl or  
 alkaryl group which is optionally substituted by a  
 35 halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro,  
 amino, aminoalkyl, acylamino, heteroaryl,  
 heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

- 6 -

$R^4$  represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

5 and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

Formula II includes galantamine itself.

10 Particularly preferred is galantamine itself, and salts thereof such as halides for example galantamine hydrobromide and the use of these compounds in the manufacture of a medicament for combatting ADD provides a further aspect of the invention.

15 Among these compounds are those described in EP-A-236684 and WO88/08708, the disclosures of which are incorporated herein by reference. Galantamine and its derivatives of formula I and II may be prepared by the methods described in these publications.

20 The cholinesterase inhibitors for use in the invention include compounds which are functionally similar to galantamine. These are defined herein as compounds which possess an at least 10-fold selectivity, preferably an at least 20-fold selectivity, more preferably an at least 40-fold selectivity, and most 25 preferably an at least 50 fold selectivity, for acetylcholinesterase as opposed to butyryl-cholinesterase, when measured by the in vitro method of Thomsen and Kewitz: Selective Inhibition of Human Acetylcholinesterase by Galantamine in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and 30 T. Thomsen, H. Kewitz and O. Pleul, J. Clin. Chem. Clin. Biochem. 26 469-475 (1988). The in vitro test described by Thomsen and Kewitz in Life Sciences, Vol 46, pp 1553-1558 (1990) is the one referred to herein whenever 35 numeric (10-fold, 20-fold, 40-fold) reference to selectivity for acetylcholinesterase as opposed to butyrylcholinesterase is made. According to Thomsen and Kewitz, galantamine hydrobromide, when tested under the

- 7 -

conditions described, shows a 50-fold selectivity; this selectivity value is taken as the "fix-point" whenever in vitro selectivities are discussed herein and could be used, for the purpose of determining the selectivities 5 for other cholinesterase inhibitors, as a calibration value which is the one to establish with galantamine hydrobromide in any repetition of the experiment described by Thomsen and Kewitz. Thus, with reference to this determination method, a preferred 10 acetylcholinesterase inhibitor is one which in the in vitro method described has an at least 10-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, such as an at least 20-fold selectivity for acetylcholinesterase as opposed to 15 butyrylcholinesterase, e.g. an at least 40-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. A selectivity test is commercially available (from Sigma Diagnostics).

For use in the method of the invention the 20 cholinesterase inhibitor such as galantamine and derivatives and salts thereof may be formulated according to conventional methods of pharmacy, together where appropriate with one or more pharmaceutically acceptable carriers, excipients or diluents such as, for 25 example, are described in Remingtons Pharmaceutical Sciences. Such formulations may for example take the form of tablets, capsules, solutions, or lozenges, pessaries, creams, suppositories or transdermal formulations such as patches, creams, ointments or 30 lotions, depending upon the administration route to be used, which may include enterally or parenterally, including orally or injection via the intravenous, intramuscular or subcutaneous routes, or intrathecally by means of an implanted device.

35 Oral and transdermal administration routes are preferred.

Precise dosage rates and regimes will depend upon

the individual patient and may be determined by the medical practitioner based on individual circumstances. For oral administration doses may be within the range of 5-100 mg per day, such as 2 to 70 mg per day e.g. 10 to 5 30 mg. For transdermal administration galanthamine may be delivered in equivalent daily doses. For parenteral administration, dosages may be in the range of 0.1 to 100 mg per day, such as 5 to 100 mg per day, e.g. 10 to 50 mg per day, including 5 to 30 mg per day; lower 10 dosages are often preferred.

Galantamine and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable 15 compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 0.1-50 mg/ml, such as 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, such as 10-30 mg/ml, 20 especially 20-30 mg/ml of galantamine.

Cholinesterase inhibitors such as galantamine and salts thereof may be used as the sole drug in the management of ADD, or may be used together with other agents useful in managing ADD.

25 The invention will now be described with reference to the following non-limiting examples.

Example 1Formulation of tablets containing galantamine5    Composition of 1 tablet containing 1 mg galantamine

	Galantamine hydrobromide	0.001	g
	Calcium phosphate	0.032	g
	Lactose	0.005	g
10	Wheat Starch	0.0056	g
	Microcrystalline Cellulose	0.015	g
	Talc	0.0007	g
	Magnesium Stearate	0.0007	g

15    Composition of 1 tablet containing 5 mg galantamine

	Galantamine hydrobromide	0.005	g
	Calcium phosphate	0.024	g
	Lactose	0.004	g
20	Wheat Starch	0.004	g
	Microcrystalline Cellulose	0.04	g
	Talc	0.002	g
	Magnesium Stearate	0.001	g

25    Composition of 1 tablet containing 10 mg galantamine

	Galantamine hydrobromide	0.010	g
	Lactose	0.040	g
	Wheat Starch	0.0234	g
30	Microcrystalline Cellulose	0.0374	g
	Talc	0.0036	g
	Magnesium Stearate	0.0012	g
	Gelatin	0.0044	g

35    Preparation

All the tablets are prepared according to routine tabletting procedures.

- 10 -

Example 2

Treatment of patients suffering from ADD

Three patients aged 9 to 11 years diagnosed as having ADD were treated with 5 mg of galantamine given 3 times per day for a total of 14 days. After this period of time, the patients showed marked improvement of symptoms, particularly as regards attention and restlessness, as judged on an ecological behavioural scale (translated: Barkley, RA et al, Assessing situational variation in children's problem behaviours: The Home and School Situations Questionnaires, in RJ Prinz (Ed), Advances in Behavioural Assessment of Children and Families, vol 3, pp 157-176, Greenwich, CT, JAI Press, Inc).

A further cohort of two 5 year old patients with ADD have been treated and again symptoms have generally improved, especially attention, as measured by ANT (Amsterdam Neuropsychological Tests), which are standard tests that measure reaction times for different tasks.

The protocol in this case is first a baseline testing before medication and retesting after 2 days on medication and then after a week repeated testing. Ecological scales were also used before and are now being evaluated after one week after two weeks etc. for a treatment of one month duration. The following table shows a selection of results obtained for these two children before and after treatment with galantamine.

- 11 -

		Before:				After:			
		mean	Sd	miss <sup>1</sup>	Fa <sup>2</sup>	mean	Sd	miss	Fa
		<b>Patient A</b>							
5	Baseline:	685	766			727	470		
	GoNoGo	705	158	1	1	655	173	1	2
	Sustained Att.	1302	565	14	13	1222	472	4	6
	Focused Att.	1214	404			1352	434	0	
10	<b>Patient B</b>								
	Baseline:	1051	899			780	418		
	GoNoGo	804	162	2	9	766	172	3	3
	Sustained Att.	1444	721	31	29	1152	600	20	50
	Focused Att.	2444	1367	1		1166	270	3	

15

<sup>1</sup> Missed task<sup>2</sup> Failed attempt

20 This data was normalized and submitted to error analysis that showed an improvement in attention (reduction in time (msec) to complete certain tasks and with fewer errors) over 2.5 standard deviations after medication with galantamine hydrobromide 2.5 mg 3 times a day.